indirectly administering acoustic energy at one or more frequencies to an internal organ, internal tissue or vessel by applying a transducer to a first site on the human or other animal other than where transport or cell viability is to be altered;

wherein the acoustic energy is effective to alter transport or cell viability at the internal tissue, internal organ or internal vessel, [The method of claim 27] wherein the transducer is placed within a surgical incision.

Remarks

Allowable Subject Matter

The indication of allowable subject matter is greatly appreciated. Claims 31-33 have therefore been rewritten in independent form.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-25 and 27-33 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection if applied to the amended claims.

Soley to narrow issues, claims 1-25 and 27-30 have been amended to delete the references to altering cell viability, although this may be a result of altering transport as claimed.

Claim 27 has been amended to more precisely define the claimed steps as:

27. A method for altering transport of chemical or biological agents into or through an internal organ, internal tissue or vessel in a human or other animal using acoustic energy, comprising:

indirectly administering acoustic energy at one or more frequencies to an internal organ, internal tissue or vessel **by applying a transducer to a first site on the human or other animal other than where transport is to be altered;**

wherein the acoustic energy is effective to alter transport at the internal tissue, internal organ or internal vessel.

Support for the term "indirectly" is found at page 11, line 9. This has been inserted to make it clearer that the transducer generating the ultrasound is applied at a location other than where the ultrasound creates an effect, by altering transport of agents.

The preamble of claim 1 has been deleted. Claim 1 adds the additional step of feedback regulation. This step is not present in claim 27.

Claims 31-33 are drawn to specific ways in which the transducer can be applied to the first site, other than where the ultrasound generates an effect.

Rejections Under 35 U.S.C. § 102 and 103

Claims 1, 2, 10, 11, 14, 15, 17, 19, 21, and 23-28 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,113,599 to Klopotek. Claims 27, 28, and 30, were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,445,611 to Eppstein et al. ("Eppstein"). Claim 22 was rejected under U.S.C. § 103(a) as obvious over Klopotek. Claims 1-3, 5, 7, 14, 15, 18, 23, 25 and 26 were rejected under 35 U.S.C. § 103(a) as obvious over Tachibana, et al., Cancer Lett. 72(3):195-199 (1993) in combination with Klopotek. Claim 26 was rejected under U.S.C. § 103(a) as obvious over U.S. Patent No. 5,636,632 to Bommannan in view of Klopotek. Claims 1-5, 8-18, 23-26 and 29 were rejected under 35 U.S.C. § 103(a) as obvious over Eppstein in combination with Klopotek. Claim 6 was rejected under 35 U.S.C. 103 as obvious over Epstein in combination with Bommannan, et al. Claim 6 was also rejected under

U.S.C. § 103(a) as obvious over Ogden in view of Klopotek. Applicants respectfully traverse these rejections to the extent that they are applied to the claims as amended.

Klopotek

As the examiner has stated in the office action at page 2, Klopotek applies ultrasound to the skin and affects cells in the underlying layers of skin.

Klopotek does not apply a transducer to the skin and observe an effect in an internal organ or internal tissue. As demonstrated by the enclosed excerpt from a textbook ("Principles of Human Anatomy, Fifth Edition, Gerard J. Tortora) showing the skin, the examiner's interpretation of the layers of cells within the skin as being a "different tissue" is not correct. This is also apparent from the figures in Klopotek, as well as the summary of the invention at col. 1, line 55 to col. 2, line 37. Klopotek applies a transducer to the skin to elicit an effect on the skin.

Therefore Klopotek does not anticipate nor make obvious the claimed subject matter.

Eppstein

Eppstein teaches the application of ultrasound to the skin (col. 4, lines 31-59) or mucosa, to alter transport through the skin (col. 6, lines 59-62)or mucosa (col. 7, lines 1-9). The materials being transported may come from a tissue other than the skin, but the ultrasound is focused within the skin or mucosa. Materials may be transported into or out of blood but this is achieved by altering the permeability of the vessels within the skin. This is readily achieved as is evident by reference to the accompanying excerpt from Principles of Anatomy showing the arteries and veins within the skin. With respect to the statement at col. 9, lines 40-43, "the stratum corneu

and even the epidermis, dermis, and other tissues beneath it", the attention of the examiner is drawn to page 95 of the enclosed excerpt, which diagrams the skin as starting at the top with the stratum corneum, then the stratum lucidum, then the stratum granulosum then the statum spinosum, then the stratum basale (the epidermis), then the papillary region, then the reticular region (the dermis), making it clear that the reference to the tissues beneath are still part of the skin. There is no mention of any internal organ or tissue. Therefore Eppstein also does not disclose the claimed subject matter.

Bommannan

Bommannan describes applying ultrasound to skin. There is a reference to a feedback mechanism.

There is no reference in either Bommannan or Klopotek or Eppstein to applying the transducer to skin and looking for an effect in an internal tissue or organ.

Therefore the combination of Bommannan and Klopotek or Eppstein cannot make obvious claim 26 or claim 6.

Tachibana, et al.

Tachibana, et al. describes the use of ultrasound *and a photoactive cytoxic agent, Photofrin II,* to kill cells. This is quite distinct from using ultrasound directly to alter cell viability at a distant location. However, to facilitate prosecution, the claims have been amended to delete reference to altering cell viability.

Ogden

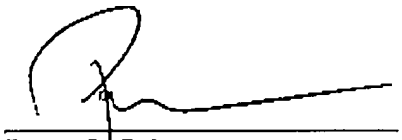
Ogden discloses administering ultrasound to the skin to enhance drug delivery through the skin. See col. 2, lines 38-58. The only membrane mentioned is the basil membrane (col. 1, lines 57-59) which is part of the skin.

There is no reference in either Ogden or Klopotek to applying the transducer to skin and looking for an effect in an internal tissue or organ.

Therefore the combination of Ogden and Klopotek cannot make obvious claim 26.

Allowance of claims 1- 6 and 8-33, as amended, is therefore earnestly solicited.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: December 13, 2002
HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)

U.S.S.N. 09/229,226
Filed: January 12, 1999
AMENDMENT AND RESPONSE TO OFFICE ACTION

Certificate of Facsimile Transmission

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being facsimile transmitted to Group 3700, Assistant Commissioner for Patents, Washington, D.C. 20231.

Patrea Pabst

Date: December 13, 2002

U.S.S.N. 09/229,226
Filed: January 12, 1999
MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

Marked Up Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (three times Amended) The method of claim 27 [for treating cells or tissues to alter permeability, cell viability or structural integrity] comprising

(a) administering acoustic energy [to the cells or tissues] at one or more frequencies ;

(b) measuring a property or the effect of the acoustic energy during the treatment with acoustic energy; and

(c) using the measurement obtained in step (b) to modify continued or subsequent application of acoustic energy [to the cells or tissues] during the treatment as needed to enhance the treatment.

2. (amended) The method of claim 1 wherein the property of the acoustic energy being measured in step b is one or more properties selected from the group consisting of pressure at one or more frequencies, and energy input at one or more frequencies.

3. (twice amended) The method of claim 1 wherein the acoustic energy is effective to alter permeability of the cells or tissues to a chemical or biological agent selected from the group consisting of peptides, proteins, sugars, polysaccharides, nucleotides, polynucleotide molecules, synthetic organic compounds, synthetic inorganic compounds, endogenous organic compounds, endogenous inorganic compounds and combinations and aggregates thereof.

4. The method of claim 3 wherein the agent is in a form selected from the group consisting of cells or virus particles, nano or microparticles, liposomes or other lipid vesicles or emulsions.

5. (amended) The method of claim 3 wherein the chemical or biological agent is delivered to cells or tissues.

6. The method of claim 3 wherein the chemical or biological agent is detected or quantitated, further comprising

removing biological fluid or molecules simultaneously, previously, or subsequently to the application of acoustic energy, and

assaying the biological fluid or molecules to detect or quantitate the chemical or biological agents.

Please cancel claim 7.

8. (amended) The method of claim 1 wherein the cells or tissues are made more permeable by the exposure to acoustic energy.

9. (twice amended) The method of claim 8 wherein the cells or tissues are made partially or completely reversibly permeable.

10. (amended) The method of claim 1 wherein the acoustic energy is applied to biological membranes.

11. (amended) The method of claim 1 wherein the tissue is skin.

12. (amended) The method of claim 1 wherein the acoustic energy is applied to cells or tissue in an amount effective to disaggregate or dissociate the cells or tissue.

13. (amended) The method of claim 1 wherein the tissues are blood vessels.

14. The method of claim 1 wherein the acoustic energy is applied at a frequency between 1 kHz and 10 MHz.

15. The method of claim 1 wherein the acoustic energy is ultrasound.

16. The method of claim 1 wherein the acoustic energy is applied at a peak positive pressure of up to 100 atmospheres.

17. (twice amended) The method of claim 1 wherein the acoustic energy is applied under conditions to effect cavitation within or on the surface of the [biological materials] cells or tissues.

18. (amended) The method of claim 1 further comprising administering an agent to enhance transport within or permeability of the cells or tissues.

19. (amended) The method of claim 1 wherein the property of the acoustic energy that is measured is measured at one or more frequencies other than the frequency or frequencies at which the acoustic energy is applied.

20. (amended) The method of claim 1 wherein the property of the acoustic energy that is measured is measured at a frequency or frequencies corresponding to integer multiples of one-half or one-fourth of the frequency applied

21. (Amended) The method of claim 1 wherein the acoustic energy is measured at one or more frequencies in the acoustic spectrum which do not correspond to peaks in the acoustic spectrum and are taken from the broadband signal of the acoustic spectrum.

22. (Amended) The method of claim 19 wherein the acoustic energy measurement is analyzed using a mathematical algorithm, selected from the group consisting of Fourier Transform and Fast Fourier Transform.

23. The method of claim 1 wherein the application of the acoustic energy is modified by changing an acoustic parameter selected from the group consisting of pressure, energy, frequency, pulse length, total exposure time, duty cycle, and combinations thereof.

24. The method of claim 1 wherein the application of the acoustic energy is modified by changing a non-acoustic parameter selected from the group consisting of temperature, fluid gas content, administration rate of molecules to be transported, sample collection rate, device position, and combinations thereof.

25. The method of claim 1 wherein the application of the acoustic energy input is modified by interrupting the application.

26. (Three times Amended) A device comprising

(a) means for treating cells or tissue by administering acoustic energy to the cells or tissue at a first site to alter permeability, cell viability or structural integrity of cells or tissues at a second distant site;

(b) means for measuring a property or the effect of the acoustic energy during the treatment with acoustic energy; and

(c) means for using the measurement of the property of the acoustic energy to modify continued or subsequent application of acoustic energy to the cells or tissues at the first site during the treatment as needed to enhance the treatment of the cells or tissues at the second distant site.

27. (three times Amended) A method for altering [cell viability or] transport of chemical or biological agents into or through an internal organ, internal tissue or vessel in a human or other animal using acoustic energy, comprising:

indirectly administering acoustic energy at one or more frequencies to an internal organ, internal tissue or vessel by applying a transducer to a first site on the human or other animal other than where transport [or cell viability] is to be altered;

wherein the acoustic energy is effective to alter transport [or cell viability] at [a distant second distant site at a different] the internal tissue [or an] , internal organ or [an] internal vessel [in a different tissue].

28. (twice Amended) The method of claim 27 wherein the acoustic energy is applied to the skin or a mucosal membrane and alters transport or cell viability at an internal organ, tissue or vessel in a different tissue.

29. (Amended) The method of claim 27 wherein the acoustic energy alters transport or cell viability of tumor cells.

30. (Amended) The method of claim 27 wherein the acoustic energy alters transport into or out of the cells of molecules selected from the group consisting of therapeutic, prophylactic and diagnostic agents.

31. (twice amended) A method for altering cell viability or transport of chemical or biological agents into or through an internal organ, internal tissue or vessel in a human or other animal using acoustic energy, comprising:

indirectly administering acoustic energy at one or more frequencies to an internal organ, internal tissue or vessel by applying a transducer to a first site on the human or other animal other than where transport or cell viability is to be altered;

wherein the acoustic energy is effective to alter transport or cell viability at the internal tissue, internal organ or internal vessel, [The method of claim 27] wherein the transducer is placed inside the body using invasive or minimally invasive means.

32. (twice amended) A method for altering cell viability or transport of chemical or biological agents into or through an internal organ, internal tissue or vessel in a human or other animal using acoustic energy, comprising:

indirectly administering acoustic energy at one or more frequencies to an internal organ, internal tissue or vessel by applying a transducer to a first site on the human or other animal other than where transport or cell viability is to be altered;

wherein the acoustic energy is effective to alter transport or cell viability at the internal tissue, internal organ or internal vessel, [The method of claim 27] wherein the transducer is placed within a blood vessel using a catheter.

33. (twice amended) A method for altering cell viability or transport of chemical or biological agents into or through an internal organ, internal tissue or vessel in a human or other animal using acoustic energy, comprising:

indirectly administering acoustic energy at one or more frequencies to an internal organ, internal tissue or vessel by applying a transducer to a first site on the human or other animal other than where transport or cell viability is to be altered;

wherein the acoustic energy is effective to alter transport or cell viability at the internal tissue, internal organ or internal vessel, [The method of claim 27] wherein the transducer is placed within a surgical incision.